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QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER	
KIM, ALEXANDER D	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/827,121	BAXTER ET AL.	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Attachment*.

DETAILED ACTION

Application Status

1. In response to the previous Office actions, a non-Final rejection (mailed on 11/07/2006), Applicants filed a response and amendment received on May 4, 2007. Said amendment cancelled Claims1-60, amended Claims 67, 68, 70, 75, 77, 79, 80, 81. Thus, Claims 61-82 are pending in the instant Office action.

Information Disclosure Statement

2. Applicants recite the references have been previously provided "from the file of application 08/764,870, now U.S. patent 6,236,946" (see middle of page 9; Remarks/Arguments). However, previous priority applications 09/637132, 08/980115 and 08/764870 do not contain copy of references in the Information disclosure statements (IDSs) filed on 01/11/2005 and 04/25/2006; thus, as noted in the previous office action the References are not considered because paper copies were not located in the prior filed applications. Examiner requests that applicant provide a copy of each reference not considered in response to this office action.

3. The information disclosure statement filed 11/13/2006 fails to comply with 37 CFR 1.97(c) because it lacks the fee set forth in 37 CFR 1.17(p). It has been placed in the application file, but the information referred to therein has not been considered.

Withdrawn-Non-Compliance with Sequence Rules

4. The previous non-compliance with Sequence Rules because of missing SEQ. ID NOs in Figure 3 is withdrawn.

Maintained-Non-Compliance with Sequence Rules

The previous non-compliance with sequence rules for structural coordinates in Appendices 3-8 without an appropriate SEQ ID NOs is maintained. Applicants must provide, as noted in the previous "Notice to Comply": a) An initial or substitute computer readable form (CRF) copy of the "Sequence Listing". b) An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**. c) A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Withdrawn-Objections to the Specification

5. The previous objection of specification for the title is not descriptive of the claims is withdrawn by the virtue of Applicants amendment.

6. The previous objection of specification of Appendix 8 in page 365 reciting "GC-2" is withdrawn by the virtue of Applicants amendment.

Withdrawn-Claim Objections

7. The previous objection of Claim 67 reciting "Forrier" is withdrawn by the virtue of Applicants amendment.

Withdrawn-Claim Rejections - 35 USC § 112

8. The previous rejection of Claims 75-82 under 35 U.S.C. 112, second paragraph, reciting the limitation "high resolution" is withdrawn by the virtue of Applicants amendment.

Maintained-Claim Rejections - 35 USC § 112

9. The previous rejection of Claims 61-82 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue the specification "provides an extensive teaching with respect to the structural and functional characteristics of the claimed genus" "including many specific working examples" for one of skill to "recognize the identity of a member of the genus" (see middle of page 10, Remarks/Arguments). Thus, Applicants argue the instant rejection is inappropriate and a "factual basis for the rejection of these claims is not present" in the instant rejection (see middle of page 11, Remarks/Arguments). Applicants further argue "Even with regard to the more generic independent claims 61 and 61, there is a sufficient description of reduction to practice and disclosure of relevant,

identifying characteristics sufficient to show Applicant was in possession of the claimed genus" (see middle of page 11, Remarks/Arguments).

However, as previously noted, the claimed methods of using structural coordinates of any nuclear hormone receptor, any thyroid receptor, any thyroid receptor isoform, or any thyroid receptor ligand binding domain, which encompasses species that are widely variant in structure (see top of page 8, the previous Office Action), is not described sufficiently by the instant specification and prior arts. Also, claims 66, 76, 78, 80 and 82 with limitation of the structural data to Appendix 3 have been interpreted as encompassing the use of those coordinates for producing any homology model, which also encompass widely variant structures. "As such, the disclosure of representative species of structural coordinates as disclosed in Appendix 3-8, which describes the three-dimensional structure of rat thyroid hormone receptor or human thyroid hormone receptor is insufficient to be representative of the attributes and features of all species of structure coordinates and models thereof encompassed by the recited genus method of using three-dimensional structure information based on any crystals or any model of structural coordinate of said receptors including any homology model." (see top of page 8, the previous Office Action). As noted above, the specification does not provide any structural information commonly possessed by members of the genus, which distinguish the species within the genus of structural coordinates or models thereof from others such that one can visualize or recognize the identity of the members of the genus. Thus, there are no correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicants were in possession of the claimed

genus. The method of Applicants method of using the coordinates in Appendix 3-8 (or models thereof) cannot be used to find a potential ligand(s) for any (or all) nuclear hormone receptor as encompassed by the claims. For the reasons above, the instant rejection is maintained.

10. The previous rejection of Claims 61-82 under 35 U.S.C. 112, first paragraph, the scope of enablement, while being enabling for a method of using a model of thyroid hormone receptor having the structural coordinates of Appendix 3-8, does not reasonably provide enablement for the broad scope of claimed method comprised of using a model of any nuclear hormone receptor, any model ligand binding domain, including any thyroid receptor or binding site thereof wherein the method steps encompass: providing structural information from a nuclear hormone receptor, which includes crystallization of a nuclear hormone receptor with or without a ligand, using structural information of a model representing a nuclear hormone receptor, or using a structural information from homology models of any nuclear hormone receptor related protein is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants allege the previous rejection "states that nothing is enabled". However, this is not true by the virtue of the previous rejection reciting being enabling for a method of using a model of thyroid hormone receptor having the structural coordinates of Appendix 3-8. Applicants argue claimed methods are fairly simple, straight forward and do not require experimentation to discover all nuclear hormone receptors, all ligands, or

all nuclear atomic coordinate data. However, the instant claims do not have such limitations to be interpreted as Applicants' argument stated above.

Examiner notes that discovering all hormone receptors, all ligands, or all nuclear atomic coordinate data is not enabled by the instant specification and the prior art without further experimentation by the one of skill in the art supported by the Applicants' analogy reciting "making sandpaper from moon dust by gluing dust particle to paper is easy to practice without experimentation even if the unclaimed starting materials are difficult or expensive to obtain" (see bottom of page 12, Remarks/Arguments). The recited analogy may be true in certain art but not in the biotech art where a binding ligands often used as pharmaceutical, which always require a certain degree of experimentation whether the experimentation is undue or not.

Applicants argue "the allegations and factual bases for the rejections of" "claims are sparse, or non-existent, no prima facie case for the rejection" except Claim 61 (see top of page 13, Remarks/Arguments) in regarding to the eight Wands factors. However, the Wands factor has been addressed adequately and properly in the previous rejection from page 9 to 15. Applicants argue the claims are not reach through claims to an as yet discovered invention, which is not supported by the disclosure nor a limitation of the instant claims. Applicants argue the breadth of the claim "is actually quite narrow to particular method steps of accessing and providing information" (see page 13, lines 19-20); but this is not reflective of the instant claim limitation. Applicants argue the claimed method includes a positive as well as a negative results; thus, the claimed "methods of assessing binding interactions are enabled well beyond the standards of the applicable

case law and regulations" (see bottom of page 13, Remarks/Argument) and the present claims are not directed to methods of crystallization. Applicants argue the specific direction and examples are present in the specification and "the quantity of experimentation is essentially zero and no undue experimentation required because "the negative results is a success in the methods" (see bottom of page 14, Remarks/Arguments) wherein the positive and negative results to be routine.

The claimed method would be a routine and does not require undue experimentation if an atomic structural coordinates of all receptor as encompassed in claimed method is available for said method step, which are determined by the X-ray crystallography, which require formation of the receptor protein crystal, which is unpredictable as known to one skilled in the art, as noted in page 11-12 of the previous office action. As noted in the previous office action page 14, top. "In this case, the specification fails to compensate for the high level of unpredictability in the art. The specification fails to teach sufficient working example of the broad claimed invention. While the specification teaches working examples of using models having the structural coordinates of Appendix 3-8, it is noted that these examples are not sufficient to enable models of all nuclear hormone receptors and their isoforms as disclosed in claims." and "applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, the modeling structure and use of modeled structure and ligand interaction to have

desired biological influence is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue" (see previous Office Action, middle of page 15).

Maintained-Double Patenting- 35 USC § 101

11. The previous rejection of Claims 76,78, 80 and 82 under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 10, 11 and 22, respectively, of prior U.S. Patent No. 6,266,622 is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue the instant amended limitation of 2-3 Å resolution employed by the instant model is not included by the U.S. Patent No. 6,266,622.

However, the U.S. Patent No. 6,266,622 recites the resolution of 2.2, 2.0, 2.1 or 2.45 which is also an inherent feature of the crystals; thus meeting all limitations of instant claims.

Maintained-Double Patenting

12. The previous rejection of Claims 61-75, 77, 79, and 81 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,266,622 is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue the present application is a CON of DIV of the U.S. Patent No. 6,266,622 and may file a terminal disclaimer.

The terminal disclaimer has not been filed. For this reason, the instant rejection is maintained.

13. The previous rejection of Claims 61-82 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,236,946 is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue "The two dimensional graphic representation of the Figures is not identical to the precise databases of the Appendices and cannot render them obvious.

However, even if the coordinates are labeled differently (i.e. Figure and Appendix), they contain identical coordinates. See below for the picture of said Figure and Appendix. For this reason, the instant rejection is maintained.

Maintained-Claim Rejections - 35 USC § 102

14. The previous rejection of Claims 61-62, 65, 67-68, 70-71, 73 and 74 under 35 U.S.C. 102(b) as being anticipated by reference by Zechel et al. (1994, March 15, The EMBO Journal, vol. 13, p. 1425-1433) as evidenced by Spanjaard et al. (1991, Proc. Natl. Acad. Sci. USA, vol. 88, p. 8587-8591) is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue the DNA of Zechel et al. binding to the DNA binding domain (DBD) "is certifiably not of a ligand to a nuclear hormone receptor ligand binding

domain(LBD). Applicants argue the standardized terminology in the field should clearly distinguishing DBD and LBD, wherein "nuclear hormone receptors as "composed of several domains which are differentially conserved between the various receptors and have different roles: ---" (see middle of page 17, Remarks/Arguments); thus, "unreasonable to confuse DBDs with LBDs in the light of this disclosure.

Examiner acknowledge "USPTO personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure" but the "Limitations appearing in the specification but not recited in the claims should not be read into the claim" (see MPEP 2106[R-5] II). The Examiner is not confused of these two domain but interpreted the instant claim reasonably broad according to the MPEP. Without the appropriate limitation(s) in the claims, wherein the limitation disclose a certain region or a domain of the nuclear receptor that is not a DNA (a ligand) binding domain of the nuclear receptor, the instant claims reciting "ligand" encompasses the DNA of Zechel et al.

As noted in the previous rejection, "an instant ligand encompasses a DNA and/or zinc of Zechel et al. teach a method of using a model of a nuclear hormone receptor and ligand binding domain" "based on the three-dimensional structure of GR (glucocoticoid receptor) and ER DBD-DNA (estrogen receptor DNA binding domain) complexes which meets the limitation of providing, accessing and modeling structural information.

Applicants argue a computationally designed ligand is not found in Zechel. However as noted previously, Zechel et al. teaches a method based on the three-

dimensional structure comprising a step of solving "the glucocorticoid receptor DNA-binding domain complexed with DNA" (see Abstract and p. 1429, Fig. 4 caption) which necessarily involves performing a Fourier transformation of crystallographic data through computation, thus a method of Zechel et al. meet the limitation of claim 67 as well as Claim 71. Applicants also acknowledge the nuclear hormone receptors can be "ligand-activated transcription factors that regulate gene expression by interacting with specific DNA" (emphasis added, see page 19, last line, Remarks/Arguments). For the reasons above, the instant rejection is maintained.

15. The previous rejection of Claims 61-65, 67-69, and 71-73 under 35 U.S.C. 102(b) as being anticipated by McKinney, James D. (1989, Environmental Health Perspectives, vol. 82, p. 323-336) is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue that the paragraph (as shown as figures below) have no "disclosure that can reasonably be interpreted as stated in the Action". Applicants argue "it is not logical, based on the disclosure" of instant specification page 16, bottom - page 17, top (as shown in two figures below) "to suggest that any protein that binds the same ligand as a nuclear receptor can be considered to be a nuclear receptor" (see top of page 19, Remarks/Arguments). Are Applicants trying to say a protein that binds to a nuclear receptor ligand listed in the specification is not a nuclear receptor protein?. It is unclear of arguments above.

29 APPLICABILITY TO NUCLEAR RECEPTORS
30 The present invention, particularly the computational methods, can be used to design
31 drugs for a variety of nuclear receptors, such as receptors for glucocorticoids (GRs),

1 androgens (ARs), mineralocorticoids (MRs), progestins (PRs), estrogens (ERs), thyroid
2 hormones (TRs), vitamin D (VDRs), retinoid (RARs and RXRs), icosanoid (IRs), and

According to the instant specification, as shown above, the thyroid hormones receptor (shown by the arrow above) is one of many nuclear receptors. The recitation of "can be considered to be a nuclear receptor" in the Remarks/Arguments has been treated as ---can be considered to be a nuclear receptor protein---. In view of the instant specification, the thyroxine binding prealbumin (TBPA), which binds to the thyroid hormone (thyroxine) binding protein (i.e., TBPA) of the McKinney et al.; thus, TBPA is a nuclear hormone receptor protein for thyroxin which is encompassed by the term nuclear hormone receptor protein by the instant specification.

Applicants argue the TBPA is a "serum transport protein" according to page 327, which is not a nuclear protein and also argue "even if it were true, would not teach the present invention". Applicants argue McKinney does not teach all limitations comprising: providing structural information, accessing structural information or modeling binding of the potential ligand. Applicants argue the McKinney "does not use proactively use of a model to computationally design ligands". Applicants recite "even a layman would understand that a protein floating free in the blood stream is not a nuclear protein" as if a claimed nuclear protein is limited to a membrane protein, which is not true in this case.

Applicants acknowledge that TBPA have properties in common or aspects of similarity with at least one thyroid hormone nuclear receptor and there is no indication or a teaching that "serum transport protein" (as recited in the Remarks/Arguments, page 19, middle) cannot be encompassed by a very broad term (as disclosed above) a "nuclear hormone receptor", especially wherein the TBPA was extracted from the "rat liver nuclear extract" as noted in the previous office action. The instant claimed nuclear receptor protein is not limited to the membrane bound protein; thus, a TBPA protein floating freely is encompassed by the claimed nuclear receptor protein. As noted in the previous office action, "McKinney teach that "the binding site matches the structure and chemistry of the hormone with great precision, which together with the fact that TBPA almost completely engulfs the hormone" (see top of left column, p. 328, lines 6-9)" which meets the limitations of providing, accessing and modeling binding of potential ligand (hormone) of the structure coordinates. "The structure model of McKinney is based on high-resolution X-ray crystallographic structure (see p. 329, Figure 3 caption), which necessarily used a Fourier transformation of X-ray crystallographic data" which meets the limitations of providing, accessing and modeling binding of potential ligand (hormone) of the structure coordinates. In figure 3 of McKinney shows "the nonphenolic (tyrosyl) ring of THs (thyroid hormones) appears to be suitable (somewhat rigid, sterically accessible aromatic ring that is polarizable) for undergoing a stacking interaction" (see top of right column, p. 328, lines 14-19) and interaction of ligands (four different ligands) in the binding pocket meet the limitations of "modeling binding of the potential ligand" (Claim 62) which encompassing the step of "proactively use of a model

to computationally design ligands" as disclosed in the bottom of page 20, Remarks/Arguments. As noted previously, the Thyroxine (T3) used in modeling by McKinney has all the chemical features required by the instant Formula 1 disclosed in the instant specification page 3, which is a nuclear receptor ligand likely to bind to a nuclear hormone receptor ligand binding domain (as recited in the claim). For the reasons above, the instant rejection is maintained.

Maintained-Claim Rejections - 35 USC § 103

16. The previous rejection of Claims 66, 76, 78, 80 and 82 under 35 U.S.C. 103(a) as being unpatentable over McKinney, James D. (1989, Environmental Health Perspectives, vol. 82, p. 323-336) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004) is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue the instant rejection should be withdrawn because the McKinney et al "does not teach all limitations of the independent claims, neither does it teach all limitations of the associated dependent claims" (see middle of page 21, middle, Remarks/Arguments. Applicants also argue the cited case law is irrelevant to the present claims because the claims are not to a device , but to methods. Applicants argue "the claims at issue are not "mere compilations of data", but claims to methods functionally incorporating structural data to prove a *useful* output" (see top of page 22, Remarks/Arguments) and recites "It can not be said that the data are non-functional in the method. Applicants further argue that the atomic coordinate data has been shown

to function.

However, machine readable data is a non-functional descriptive material. The instant coordinates which are processed using a series of processing steps using a known algorithm, do not appear to impose a change in the processing steps or functioning of the computer and there is no evidence of record that the data of Appendix 3 imposes a change in the function of the computer. Put another way, the function of the computer is the same whether the computer comprises the Appendix 3 or not. Thus, all claim limitations concerning the structure coordinate data of Appendix 3 are given no patentable weight as the data is considered to be non-functional descriptive material. As noted in the previous office action and above, the McKinney et al. meets all limitation of method steps except the Appendix 3, which is non-functional descriptive material with no patentable weight. Therefore, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ the method as disclosed by McKinney using any set of structural coordinates as defined in the claims with a reasonable expectation of success in view of the teachings of McKinney. One would have been motivated to do this because McKinney discloses "The multifunctional ligand-receptor model concept should also be considered in the study of structure-activity relationships --- for other hormonal systems such as the steroid hormones" (see page 333, right column, bottom), wherein McKinney notes that "TBPA and at least one thyroid hormone nuclear receptor have a considerable number of their properties in common or have aspects of similarity" (see page 330, left column, lines 14-16) and further notes that "Studies of TBPA and the

thyroid hormone nuclear receptor suggested that possibility of a closer relationship between the two proteins than would have been anticipated, which suggests that the studies on TBPA may have a direct bearing on the properties of the nuclear receptor" (see p. 327, right column bottom). For the reasons above, instant rejection is maintained.

17. The previous rejection of Claims 75, 77, 79, and 81 under 35 U.S.C. 103(a) as being unpatentable over McKinney, James D. (1989, Environmental Health Perspectives, vol. 82, p. 323-336) is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue McKinney et al. do not teach at least one limitations of claims as recited in the bottom of page 23 of Remarks/Arguments and also argue the TBPA is different from the claimed TR (thyroid hormone receptor) isoform; thus, "TBPA is not a model for TR interactions" (see page 24, line 21, Remarks/Arguments) even though Applicants acknowledge McKinney makes it clear that TBPA models help provide general concepts of the binding interactions. Applicants also argue "one skilled in the art working on the problem of the claims" for "identifying compounds that "selectively modulates the activity of a TR" would not be motivated by McKinney because the TR and TBPA have different selectivity and affinity for thyroid hormones. Thus, "there would not be an expectation of success"

However, as noted above and in the previous office action, the TBPA of McKinney et al. is encompassed by the claimed "thyroid hormone receptor (TR)

isoform" as recited in the claims. The instant claims have amended limitation of resolution to 2.0 Å to 3.0 Å, which is not disclosed by the McKinney et al. However, as it is written in claims, the said resolution is "corresponding to an atomic coordinate model" (emphasis added), wherein the resolution is a property measured from an actual crystal by X-ray crystallography. Thus, any resolution corresponding to an atomic coordinate model, which can be generated in silico, is met by any structure coordinate. The instant claims are different from above reciting "capable of selectively modulating", which is a preamble which do not effects the limitation of claimed method step. As noted in the previous office action, "It would have been obvious to one of ordinary skill in the art at the time the invention was made to screen a test compound of McKinney to a TR LBD isoform with a reasonable expectation of success because a test compound is identified to have favorable interaction as indicated in receptor model shown in Figure 5, p. 331. The motivation to do so is provided by McKinney's disclosure of thyroid hormones "has recently been suggested --- be part of the hormone responsive transcription factor super-family" (see page 330, middle of right column) and further that one would have validated the modeling results of McKinney with a biological assay. Thus, the claimed invention taken as a whole is *prima facie* obvious over the combined teachings of the prior art." (see page 21 to 22 of the previous office action). For the reasons above, the instant rejection is maintained.

Summary of Pending Issues

18. The following is a summary of the issues pending in the instant application:

a) The previous non-compliance with sequence rules for structural coordinates in Appendices 3-8 without an appropriate SEQ ID NOs is maintained.

b) The previous rejection of Claims 61-82 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained.

c) The previous rejection of Claims 61-82 under 35 U.S.C. 112, first paragraph, the scope of enablement, is maintained.

d) The previous rejection of Claims 76,78, 80 and 82 under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 10, 11 and 22, respectively, of prior U.S. Patent No. 6,266,622 is maintained.

e) The previous rejection of Claims 61-75, 77, 79, and 81 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,266,622 is maintained.

f) The previous rejection of Claims 61-82 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,236,946 is maintained.

g) The previous rejection of Claims 61-62, 65, 67-68, 70-71, 73 and 74 under 35 U.S.C. 102(b) as being anticipated by reference by Zechel et al. (1994, March 15, The EMBO Journal, vol. 13, p. 1425-1433) as evidenced by Spanjaard et al. (1991, Proc. Natl. Acad. Sci. USA, vol. 88, p. 8587-8591) is maintained.

h) The previous rejection of Claims 61-65, 67-69, and 71-73 under 35 U.S.C. 102(b) as being anticipated by McKinney, James D. (1989, Environmental Health Perspectives, vol. 82, p. 323-336) is maintained.

i) The previous rejection of Claims 66, 76, 78, 80 and 82 under 35 U.S.C. 103(a) as being unpatentable over McKinney, James D. (1989, Environmental Health Perspectives, vol. 82, p. 323-336) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004) is maintained.

j) The previous rejection of Claims 75, 77, 79, and 81 under 35 U.S.C. 103(a) as being unpatentable over McKinney, James D. (1989, Environmental Health Perspectives, vol. 82, p. 323-336) is maintained.

Conclusion

19. Claims 61-82 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered section in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alexander Kim
July 18, 2007

RICHARD HUTSON, PH.D.
PRIMARY EXAMINER

Attachment.

Left column shows Appendix 3 of instant application, right column shows Figure of US Patent 6236949).

APPENDIX 3

TR_DMT.PDB

```
REMARK TR_dmt full length numbering
REMARK
REMARK Rfactor 0.205 Rfree 0.227
REMARK Resolution 15. 2.2 all reflections
REMARK
REMARK Three cacodylate-modified cystrines (CYA)
REMARK Cya334, Cya380, Cya392
REMARK cacodylate modeled as single arsenic atom
REMARK
REMARK side chain of certain residues modeled as ALA due to poor density;
REMARK however, residue name reflects true residue for clarity
REMARK
REMARK clone obtained from Murray et. al.
REMARK deposited sequence confirmed,
REMARK differing from that reported by Thompson et. al.
REMARK in the following codons:
REMARK 281 Thr - Ala
REMARK 285 Lys - Glu
REMARK identical to that reported by Mitsuhashi et. al.
REMARK gb:RNTRAVI X07409
JRNL      AUTH  M.B. MURRAY, N.D.ZILZ, N.L.MCCREARY,M.J.MACDONALD
JRNL      AUTH 2 H.C.TOWLE
JRNL      TITL  ISOLATION AND CHARACTERIZATION OF RAT CDNA CLONES
FOR TWO
JRNL      TITL 2 DISTINCT THYROID HORMONE RECPTORS
JRNL      REF   JBC                V. 263 25  1988
JRNL      AUTH  C.C.THOMPSON, C.WEINBERGER, R.LEBO, R.M.EVANS
JRNL      TITL  IDENTIFICATION OF A NOVEL THYROID HORMONE RECEPTOR
EXPRESSED
JRNL      TITL 2 IN THE MAMMALIAN CENTRAL NERVOUS SYSTEM
JRNL      REF   SCIENCE            V. 237  1987
JRNL      AUTH  T.MITSUHASHI,G.TENNYSON,V.NIKODEM
JRNL      TITL  NUCLEOTIDE SEQUENCE OF NOVEL CDNAS GENERATED BY
ALTERNATIVE
JRNL      TITL 2 SPLICING OF A RAT THYROID HORMONE RECEPTOR GENE
TRANSCRIPT
JRNL      REF   NUC. ACIDS. RES.   V. 16 12  1988
ATOM   1  N  ARG  157     68.504  8.445  5.651  1.00 68.93
ATOM   2  CA ARG  157     67.886  9.543  6.398  1.00 56.98
ATOM   3  CB ARG  157     68.769 10.789  6.324  1.00 59.25
ATOM   4  CG ARG  157     70.147 10.632  6.932  1.00 58.90
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FIG. 28

```
REMARK TR_dmt full length numbering
REMARK
REMARK Rfactor 0.205 Rfree 0.227
REMARK Resolution 15. 2.2 all reflections
REMARK
REMARK Three cacodylate-modified cystrines (CYA)
REMARK Cya334, Cya380, Cya392
REMARK cacodylate modeled as single arsenic atom
REMARK
REMARK side chain of certain residues modeled as ALA due to poor density;
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ATOM   2  CA  ARG  157     67.886  9.543  6.398  1.00 56.98
ATOM   3  CB  ARG  157     68.769 10.789  6.324  1.00 59.25
ATOM   4  CG  ARG  157     70.147 10.632  6.932  1.00 58.90
ATOM   5  CD  ARG  157     70.068 10.422  8.425  1.00 59.37
ATOM   6  NE  ARG  157     71.392 10.446  9.036  1.00 63.94
ATOM   7  CZ  ARG  157     71.613 10.329 10.341  1.00 64.39
ATOM   8  NH1 ARG  157     70.596 10.182 11.179  1.00 62.14
ATOM   9  NH2 ARG  157     72.853 10.365 10.808  1.00 65.56
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